

AMRL-TR-65-49

AD 617 691
Citation

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FRANCIS W. WEIR
FREDERICK H. MEYERS
ROBERT H. ARBUCKLE
SWANSON BENNETT

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MAY 1965

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**FRANCIS W. WEIR
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FOREWORD

The research was performed under Contract AF 33(657)-11756 in support of Project 6302, "Toxic Hazards of Propellants and Materials," Task 630202, "Pharmacology and Biochemistry," from September 1963 to September 1964 for the Toxic Hazards Branch, Physiology Division, Biomedical Laboratory, Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, Ohio.

Mr. F. W. Weir was the principal investigator and C. H. Hine, M.D., was technical consultant for The Hine Laboratories, Inc., San Francisco, California. K. C. Back, Ph.D., was contract monitor for the Aerospace Medical Research Laboratories.

The authors are grateful to W. F. Ganong, M.D., who provided consultation; to A. Halevy, Ph.D., who performed the biochemical analysis of serotonin; and to Mr. W. G. Blucher and Mr. J. H. Nemenzo, who provided invaluable technical services.

This technical report has been reviewed and is approved.

WAYNE H. McCANDLESS
Technical Director
Biomedical Laboratory

ABSTRACT

This investigation was conducted to establish the mechanism of toxic action of pentaborane (B_5H_9) and decaborane ($B_{10}H_{14}$) preliminary to the study of possible therapeutic or protective agents. The pharmacological effects of pentaborane and decaborane on mice, rats, and dogs were studied and compared to the pharmacological effects of reserpine. The compounds were administered intraperitoneally; pentaborane was also administered by the inhalation route. Conscious dogs showed signs of limitation of sympathetic activity, evidenced by miosis, nictitating membrane relaxation, bradycardia, dilation of superficial vessels, and sedation with easy arousal. Anesthetized dogs showed an initial rise in blood pressure followed by hypotension, bradycardia, and decreased response to tyramine. Reversal of some of these effects occurred following norepinephrine infusions. Spectrofluorometric analyses of the brains of groups of rats administered any of the three compounds demonstrated depletion of serotonin and norepinephrine. Pentaborane is comparatively more active in producing excitement and convulsions. The boranes closely resemble reserpine in their effects but have a shorter duration of action.

SECTION I

INTRODUCTION

The present investigation sought to establish the toxic action of pentaborane (B_5H_9) and decaborane ($B_{10}H_{14}$) preliminary to the study of possible therapeutic or protective agents.

Prior investigations of the toxic actions of pentaborane failed to relate its effects to those of any well studied class of drugs or toxicants. Sedation was observed in animals (Ref. 1), but most investigators have used convulsions as an index of toxicity. Therefore, our initial experiments were aimed at determining whether pentaborane parallels the action of any familiar drug group.

Clinical reports (Refs. 2,3,4) of the sequelae of human exposure to the boranes describe lethargy, loss of memory, irresponsibility, slurred speech, poor coordination, and drowsiness. These effects are often associated with central nervous system depression. The clonic movements, muscle spasms, opisthotonos, catatonia, and blurred vision also reported may be reinterpreted as evidence of extrapyramidal and autonomic effects. Thus, the order of experiments was further influenced by the assumption that the boranes are tranquilizers.

This assumption was shown to be valid and a mechanism of action similar to reserpine was established for these inorganic reducing agents.

SECTION II

MATERIALS AND METHODS

Mice and rats were exposed to pentaborane vapors in a 215.0-liter cylindrical, dynamic-flow chamber operated at a flow rate of 75.0-100.0 l/min. Pentaborane was dispersed and the concentrations in the atmosphere were monitored by methods similar to those described by Weir et al. (Ref. 5).

Liquid pentaborane for injection was transferred from the shipping container to a special holding flask by positive-pressure vapor transfer and freeze-out techniques. The holding flask and subsequent direct injection procedures were similar to those reported by Dost et al. (Ref. 6). Decaborane, as a solution in 45% (v/v) ethanol, was injected intraperitoneally in dogs. Solutions of decaborane in mineral oil and in corn oil were used on rats as detailed below. Except for reserpine, which was suspended in a water-gum ghatti-propylene glycol mixture, other compounds were in aqueous solutions.

1. Pentobarbital Sleeping Time of Mice Exposed to Pentaborane.

Groups of 10 mice each were injected intraperitoneally with sodium pentobarbital at 1, 8, 18, or 24 hours after 30 minute exposures to pentaborane. Sleeping time was measured as the interval between injection of the pentobarbital and the time an animal righted itself twice.

2. Effect of Graded, Intraperitoneal Doses of the Boranes and Reserpine on Conscious Dogs.

Following a control period, conscious dogs were injected with graded, intraperitoneal doses of pentaborane, decaborane, or reserpine. Behavior was observed and indices of cardiovascular and autonomic nervous system function measured. The male, mongrel dogs were retained in individual, fiberglass cages for observation. External stimulation was minimal except during examinations.

3. Cardiovascular and Autonomic Effects in Anesthetized and Conscious Dogs.

The cardiovascular and autonomic effects of the boranes and reserpine were studied in anesthetized dogs following two schedules of intraperitoneal injections. In the first series of experiments dogs were anesthetized and control observations, including physiological reflex tests and challenges with various drugs, were made. Pentaborane, decaborane, and reserpine were then given and observations continued or repeated. In a second series of experiments, animals were given two injections of pentaborane, decaborane, or reserpine at 48 and 24 hours before the recordings were made.

Observations were also made following acute exposure to pentaborane by inhalation.

All measurements were recorded on a Grass polygraph. Standard electrocardiographic leads were used.

a. Blood Pressure: Recorded from a femoral artery through a polyethylene catheter connected to a transducer.

b. Respiration: Recorded from an endotracheal tube attached to a pneumotachygraph.

c. Carotid Occlusion: Following exposure, both common carotid arteries were occluded for 20 seconds with rubber-sheathed hemostats.

d. Vagal Stimulation: Following exposure, the right vagus was stimulated with platinum wire electrodes for five second periods with 7v, 100 cps, 5 millisecc waves.

e. Drug Injections: The following drugs were injected directly into the exposed femoral vein:

- (1) tyramine-50 mcg/kg
- (2) epinephrine-5 mcg/kg
- (3) norepinephrine-1 mcg/kg/min

Unanesthetized dogs were exposed to pentaborane by inhalation. Prior to exposure, these animals were lightly anesthetized with chloroform to permit insertion of a catheter into the femoral artery and of an endotracheal tube through a tracheostomy. Following recovery from the volatile anesthetic, animals breathed a mixture of pentaborane in air from a reservoir through the endotracheal tube.

4. Effects of the Boranes and Reserpine on the Monamines in the Central Nervous System of Rats.

Male, Sprague Dawley rats (175.0-225.0 gms) were exposed to or injected with either the boranes or reserpine.

The subjects were killed by decapitation at 3, 6, 12, 24, 48, 72, and 96 hours after administration of the compounds. Brains were immediately removed; the cerebellum and cerebral hemispheres were trimmed away so that only the midbrain including the hypothalamus remained; the remaining brain structure was then weighed, and prepared for extraction.

5-Hydroxytryptamine (serotonin) was extracted and measured by a procedure modified from the method of Bogdanski et al. (Ref. 7). The brain tissue was homogenized in approximately 7.0 ml 0.1 N HCl. To the homogenate was added 5.0 gm NaCl; 10.0 ml borate buffer, pH 10.0; 1.0 ml of a freshly prepared solution of 3% ascorbic acid in 1% ethylenediaminetetraacetic acid; and 20.0 ml n-butanol. The samples were then briefly shaken and centrifuged. 18.0 ml of the supernatant butanol extract was transferred to a centrifuge tube

containing 1.0 ml of 0.1 N HCl and 25.0 ml heptane. After shaking and centrifuging, the upper solvent layer was discarded, and 1.0 ml of the acid phase was transferred to a test tube. Reagent grade perchloric acid (0.3 ml) was added and the fluorescence of samples measured at 545.0 mu in an Aminco-Bowman Spectrophotofluorometer with excitation at 295.0 mu. Recoveries were based on standards run simultaneously.

Norepinephrine was extracted and analyzed by the Shore and Olin method (Ref. 8), except that during the color development stage, samples were irradiated under a wide-band ultraviolet lamp for 10 minutes to insure a consistently maximal production of fluorescence (Ref. 9).

SECTION III

RESULTS

1. Pentobarbital Sleeping Time of Mice Exposed to Pentaborane.

Mice exposed to 8.5-9.0 ppm pentaborane for 30 minutes and subsequently tested with 30.0 mg/kg pentobarbital at the following times showed median sleeping time (95% confidence limits in parentheses) of:

1 hour after exposure:	52.0 min.	(46.0-58.8)
18 hours after exposure:	18.5 min.	(13.0-27.2)
24 hours after exposure:	16.5 min.	(11.4-23.9)
Unexposed Controls:	19.0 min.	(13.4-27.0)

Mice exposed to 3.5-4.0 ppm pentaborane for 30 minutes were similarly tested after a 45.0 mg/kg dose of pentobarbital with the following results:

1 hour after exposure:	115.0 min.	(111.0-120.0)
8 hours after exposure:	117.0 min.	(93.6-146.3)
18 hours after exposure:	88.0 min.	(67.0-117.0)
24 hours after exposure:	58.0 min.	(49.1- 68.4)
Unexposed Controls:	74.0 min.	(63.2- 86.6)

The data indicate that sleeping time was prolonged due to pentobarbital after exposure to pentaborane. The prolongation occurred between 1 and 18 hours after exposure, with the maximal effect occurring about 8 hours after exposure.

2. Effect of Graded, Intraperitoneal Doses of the Boranes and Reserpine on Conscious Dogs.

The classification of a drug or toxic agent and an understanding of its effects are often possible only when its action is observed over a range of doses. For example, the excitement observed after administration of small doses of ether or a barbiturate is understandable only when compared with the general anesthetic effects seen at high doses.

In the experiments in this series the boranes were injected intraperitoneally. Direct injection is advantageous in that accurate, graded doses may be administered. The inhalation route of exposure gives less reliable dosage information.

a. Pentaborane:

Five dogs injected intraperitoneally with 0.6-3.6 mg/kg liquid pentaborane showed behavioral changes at all dose levels. Signs of excitement

gave way to signs of depression as doses increased. Autonomic changes consisted of miosis, ptosis, injection of the gingival mucosa, extension of the nictitating membrane, irregular cardiac rate (exaggerated sinus arrhythmia) and bradycardia.

In the animal that received 0.6 mg/kg, decreased activity became apparent about 15 minutes after injection. Generally the animal slept if undisturbed, but was easily aroused; at other times it became cataleptic. Miosis was maximal; when ptosis appeared the nictitating membrane covered a third or more of the cornea; the gingival mucosa and conjunctiva were injected.

In the three animals that received the intermediate doses (1, 2, 1.2, and 2.4 mg/kg), there were, in addition to the changes described above, a marked lowering of respiratory and cardiac rates together with alternating periods of depression and excitement lasting 24-36 hours. The dog given 2.4 mg/kg died six days after injection, apparently from unrelated causes. All other animals survived.

The animal that received 3.6 mg/kg pentaborane exhibited immediate transient excitement which lasted for the first 10-12 minutes; this was followed by a period of depression between 15-45 minutes; convulsions occurred after one hour. Alternating depression and excitement persisted for about 36 hours.

b. Decaborane:

Ten dogs were injected intraperitoneally with decaborane in corn oil at doses of 2.5, 5.0, 10.0, 20.0, and 40.0 mg/kg. The subjects showed behavioral changes at all doses.

Even at the lowest doses of 2.5 and 5.0 mg/kg, the dogs became quiet and sedated within 30 minutes after injection. No further signs were observed in the two dogs injected at 2.5 mg/kg except in one dog that developed diarrhea which lasted for 24 hours.

At the doses of 5.0 and 10.0 mg/kg, depression and tranquility were seen, accompanied by emesis in several dogs within 50 minutes of injection, and ptosis within 2-3 hours. During the 5-hour observation period following injection, 2/4 subjects at these dose levels showed a weak pulse and relaxed nictitating membranes.

Ataxia and depression were apparent within a very few minutes in the two animals injected with 20.0 mg/kg. In one dog emesis occurred within about 30 minutes and diarrhea was evident within 12 hours. Both of these dogs died between 48 and 72 hours after injection.

The dogs injected with 40.0 mg/kg showed immediate depression followed by emesis. One dog died within three hours, the other overnight. No excitement, aggression, or convulsions were noted in either these animals or the animals injected with 20.0 mg/kg.

c. Reserpine:

Eight intact dogs injected intraperitoneally with reserpine in graded doses of 2.5-10.0 mg/kg showed responses generally similar to those seen with decaborane except that no deaths occurred. Exceptions to the pattern

of toxicity included less depression and considerably more diarrhea in these animals than decaborane. The time of onset of effects of reserpine was also somewhat slower and the depression lasted 72-96 hours.

3. Cardiovascular and Autonomic Effects in Anesthetized and Conscious Dogs.

a. Pentaborane:

Four dogs were given intraperitoneal injections of pentaborane in doses of 1.2-3.6 mg/kg. The usual immediate change in mean arterial blood pressure was a rise of 10.0-20.0 mm mercury at 2-5 minutes. Thereafter, pressure fell slowly but persistently, to a minimum value approximately 25.0 mm below control. Bradycardia appeared even in those animals with increased rate and elevated pressure secondary to the pentobarbital anesthesia.

As hypotension and bradycardia developed, the hypertensive response to bilateral carotid occlusion diminished, as did the pressor and chronotropic responses to injected tyramine. During the time when these responses were at a decreased level, as late as five hours after injection, the pattern of effects from vagal stimulation were unaltered and epinephrine induced an effect at least as great as during the control period. Vagal section prior to administration of the propellant to one dog and after hypotension and bradycardia had developed in another did not modify the response to pentaborane.

One dog received 1.2 mg/kg pentaborane intraperitoneally on two successive days. On the third day, after pentobarbital anesthesia, this animal showed blood pressure and heart rate lower than **generally** observed in normal control animals after pentobarbital anesthesia alone. The dog was responsive to injected epinephrine but tyramine injections and bilateral carotid occlusion produced no effect. The animal was given 1.0 mcg/kg/min norepinephrine infusions during two 20-minute periods. Long after all direct norepinephrine action should have dissipated, pressures and pulse rate were above control animal levels. Moreover, responsiveness to carotid occlusion and tyramine injections was partially restored.

Eight dogs were exposed to 14.0-28.0 ppm pentaborane for 30- or 60-minute periods. After exposure to inhalation of the lower concentrations, the dogs were cooperative and quiet to a degree suggestive of sedation. After exposure to higher levels, nausea, tremors, and convulsions interfered and forced the use of anticonvulsant doses of pentobarbital. Defecation and miosis were also observed. In the conscious animals following inhalation, a fall of 50.0 mm mercury occurred 180 minutes after exposure. Bradycardia was also more marked than in the anesthetized dogs given pentaborane intraperitoneally. After inhalation, the blood pressure had returned toward normal at 240 minutes.

b. Decaborane:

Measurement of responses to tyramine, epinephrine, and carotid occlusion were obtained from three anesthetized dogs prepared for study of cardiovascular function. After injection with 10.0 mg/kg decaborane, these animals were again tested for tyramine and carotid occlusion responses.

Two of the three dogs showed a marked decrease in the carotid occlusion response compared with initial measurements but none of the subjects showed a significant change in the tyramine response. There was no change in response to epinephrine.

In two dogs administered decaborane in a dose of 2.5 mg/kg, at 48 and again at 24 hours before the experiment (total dose 5.0 mg/kg), the pressor response to tyramine and bilateral carotid occlusion was decreased compared to normal control responses in untreated dogs. The infusion of norepinephrine into these animals at the rate of 1.0 mcg/kg/minute for periods up to 40 minutes resulted in an elevation of the blood pressure which continued for the term of the experiment. The response to injected tyramine and bilateral carotid occlusion on two occasions following the norepinephrine was increased 100-150% over pre-norepinephrine trials. Several administrations of epinephrine in the dose of 5.0 mcg/kg during the experiment demonstrated no change from the normal response seen.

Two dogs received 5.0 mg/kg decaborane injections at 48 and 24 hours prior to observation (total dose 10.0 mg/kg). These animals were treated as above and showed similar responses.

c. Reserpine:

A single dog received 0.5 mg/kg reserpine at 48 and 24 hours prior to the experiment. The results of tyramine injections and carotid occlusion were markedly lower than control observations. The administration of norepinephrine at 1.0 mcg/kg/min for up to 40 minutes did not increase the carotid occlusion or tyramine responses. The normal response to epinephrine was unchanged during this experimental period.

In two animals, control responses to tyramine, epinephrine, and bilateral carotid occlusion were obtained. The animals were then administered 5.0 mg/kg reserpine and retested over a period of four hours. The response to bilateral carotid occlusion was decreased in both animals after injection. Tyramine response was unchanged in one animal and potentiated in the other. There was no change in either animal in the response to epinephrine.

4. Effects of the Boranes and Reserpine on the Monamines in the Central Nervous System of Rats.

Rat brain serotonin was assayed after intraperitoneal injections of pentaborane and reserpine. Changes in rat brain serotonin and norepinephrine were measured following exposure by inhalation to pentaborane and following intraperitoneal injection of decaborane.

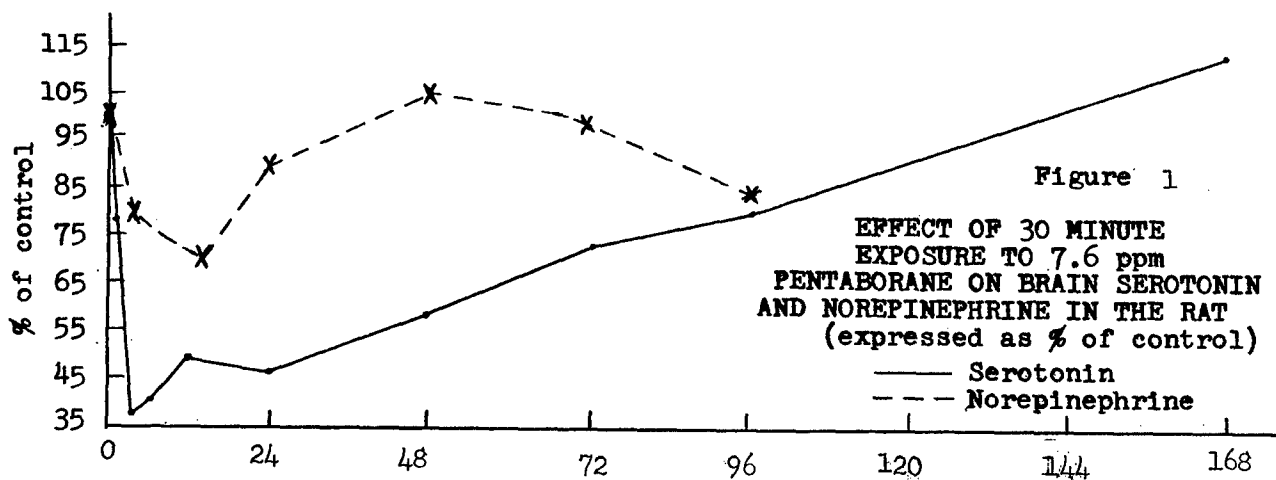
The results of the first experiment in which rats were exposed to pentaborane vapors at 7.6 ± 1.0 ppm, are shown in Table I and Figure 1. Pentaborane caused a marked depletion of brain serotonin. Maximum depletion occurred at three hours post exposure. The level of serotonin then increased linearly, reaching the level of the control animals at about six days and then continuing to a slightly higher level. Norepinephrine depletion was less marked. The rate of depletion was slower, and maximum effect occurred at 6-13 hours post exposure. The return to control level occurred at 24-48 hours post exposure.

Table I

Effect of 30-Minute Exposure to 7.6 PPM Pentaborane on Rat Brain Serotonin and Norepinephrine

Time After Exposure Hours	N	Serotonin			N	Norepinephrine		
		$\mu\text{g/gm} \pm$	S.D.	% of Control		$\mu\text{g/gm} \pm$	S.D.	% of Control
Control	20	0.48	0.07	100	30	0.35	0.05	100
1	10	*0.37	0.05	77				
3	9	*0.18	0.02	37	10	*0.28	0.03	80
6	9	*0.19	0.07	40	10	*0.26	0.05	74
12	10	*0.23	0.02	48	7	*0.25	0.04	71
24	10	*0.22	0.04	46	7	0.31	0.05	88
48	10	*0.28	0.04	58	10	0.37	0.07	106
72	9	*0.35	0.04	73	10	0.35	0.05	100
96	10	*0.38	0.04	79	10	*0.29	0.07	83
168	10	0.55	0.06	114				

*Significantly different from controls at 1% level using two-tailed t-test (Ref. 10).



The results of the second experiment, in which decaborane was injected intraperitoneally, appear in Table II and Figure 2. This compound caused an immediate decrease in norepinephrine that progressed for three hours. A return to norepinephrine control level occurred after 72 hours.

Pentaborane depleted serotonin more than norepinephrine, but decaborane depleted norepinephrine more than serotonin, although the effects of both boranes obviously overlap.

A third experiment was conducted to compare the effects of injected pentaborane with the effects of inhaled pentaborane. The effects of 8.0 mg/kg liquid pentaborane on serotonin depletion appear in Table III and Figure 3. (1) The injection and inhalation routes of administration produce remarkably similar results.

A fourth experiment was conducted to compare directly the effects of injected reserpine on the levels of brain serotonin with the effects of the boranes. The results of this experiment appear in Table IV and Figure 4. Reserpine caused the greatest degree of depression after three hours and showed no rise toward normal levels for 48 hours. At 72 hours the serotonin level was approximately 80% of control.

- (1) Incidental to this experiment, an LD₅₀ determination of liquid pentaborane in mineral oil was conducted using Sprague Dawley rats. The animals received the compound at 0.001 ml solution/gm body weight. The 24 hour LD₅₀ was 13.7 mg/kg for intraperitoneal injection. 95% confidence limits were 12.1-15.5 mg/kg as calculated by the method of Litchfield and Wilcoxon.

Table II

Effect of Decaborane (10.0 mg/kg i.p.) on Rat Brain Serotonin and Norepinephrine

Time After Exposure Hours	N	Serotonin			N	Norepinephrine		
		$\mu\text{g/gm} \pm$	S.D.	% of Control		$\mu\text{g/gm} \pm$	S.D.	% of Control
Control	20	0.48	0.07	100	10	0.72	0.11	100
3	8	0.43	0.05	90	8	*0.24	0.06	33
6					8	*0.30	0.06	42
12	8	*0.31	0.12	65	8	*0.30	0.04	42
24	8	*0.22	0.02	46	8	*0.35	0.04	49
48	8	*0.30	0.04	62	8	*0.50	0.05	70
72	8	0.44	0.07	92	8	0.67	0.03	93
96	8	0.44	0.06	92	8	0.69	0.10	95

*Significantly different from controls at 1% level using two-tailed t-test (Ref. 10).

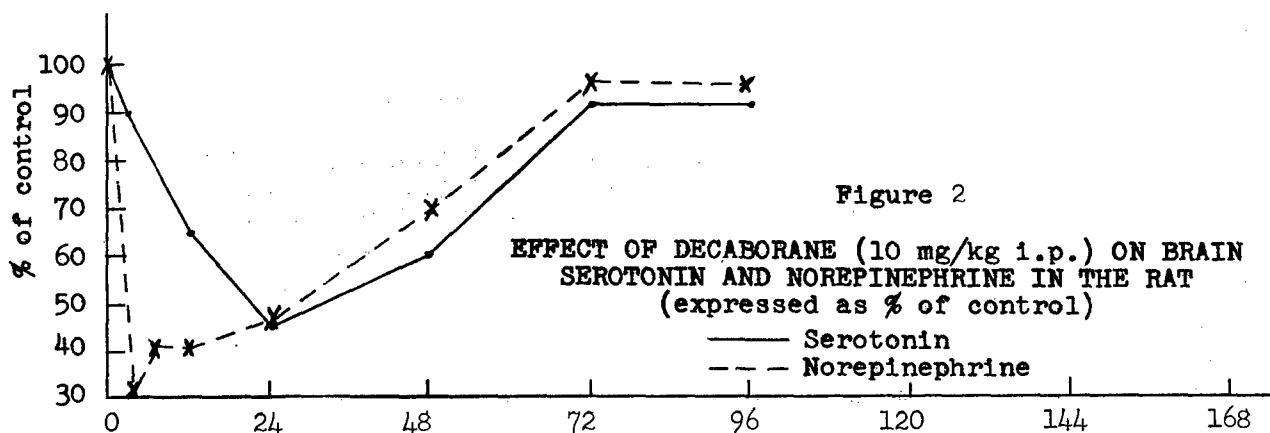


Table III

Effect of Pentaborane (8.0 mg/kg i.p.) on Rat Brain Serotonin

Time After Exposure Hours	Pentaborane				% of Control
	N	$\mu\text{g/gm}$	\pm	S.D.	
Control	20	0.48		0.07	
3	10	*0.24		0.04	50
12	8	*0.28		0.04	58
24	7	*0.27		0.05	56
48	7	*0.31		0.04	65
72	6	0.44		0.08	92
96	7	0.48		0.11	100

*Significantly different from controls at 1% level using two-tailed t-test (Ref. 10).

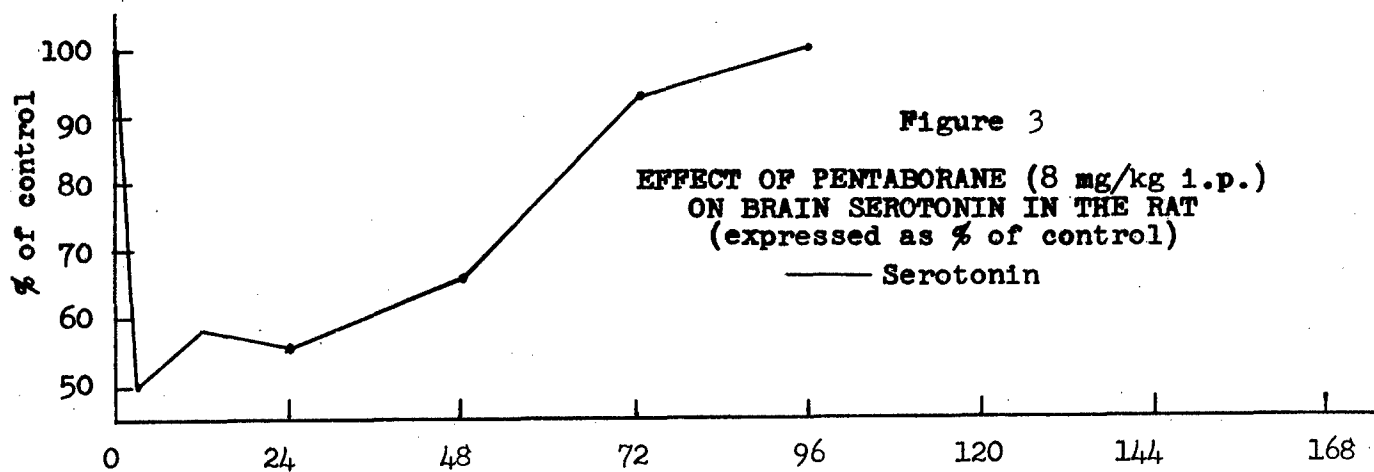
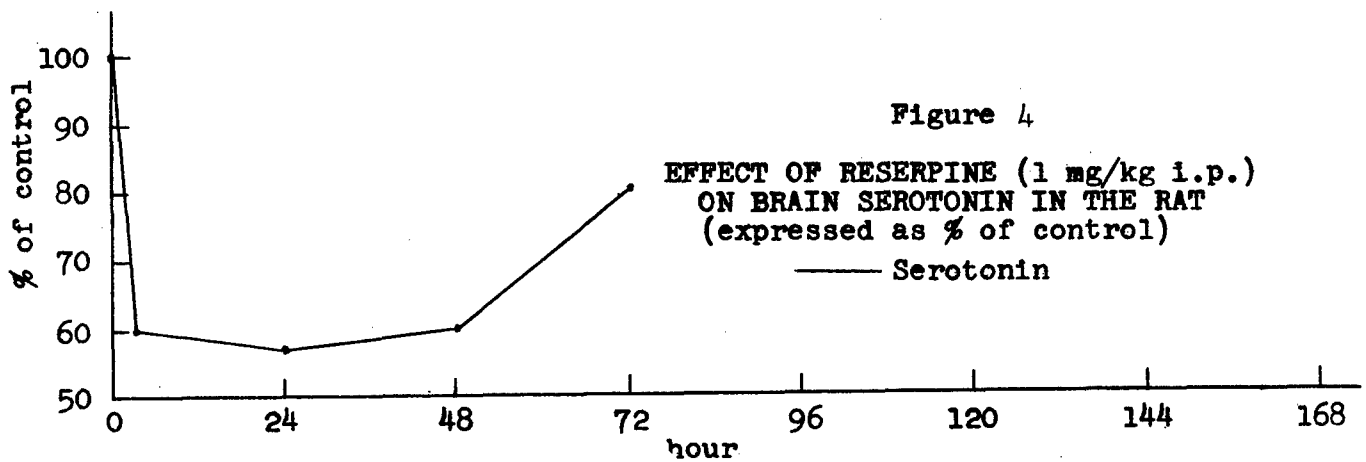


Table IV

Effect of Reserpine (1.0 mg/kg i.p.) on Rat Brain Serotonin

Time After Exposure Hours	Serotonin				% of Control
	N	$\mu\text{g/gm}$	\pm	S.D.	
Control	20	0.48		0.07	
3	7	*0.29		0.04	60.4
24	5	*0.28		0.09	58.4
48	7	*0.29		0.04	60.4
72	8	*0.38		0.06	79.2

*Significantly different from controls at 1% level using two-tailed t-test (Ref. 10).



SECTION IV

DISCUSSION

The data presented above emphasize the striking similarity in action of the boranes to reserpine, a drug which has been comprehensively studied.

1. Pentobarbital Sleeping Time in Mice Exposed to Pentaborane.

Although measurement of the effect of an agent on barbiturate-induced sleeping time is not a specific test, it may be noted that central stimulants have an analeptic effect. Amphetamine and other sympathomimetics, convulsants such as pentamethylenethylenetetrazol, and some hydrazides and hydrazines shorten sleeping time. Sleeping time is prolonged by drugs such as the sedative-hypnotics that depress the central nervous system at all levels.

A number of drugs produce manifest evidence of depression such as sleep or decreased spontaneous activity, but at the same time show neurophysiological evidence of central nervous system stimulation, including convulsions at large doses. Atropine, reserpine, and chlorpromazine, are examples of such drugs.

The initial finding that pentaborane produced extended sleeping time justified an analytic approach to the mechanism(s) of action different from other propellants which seemed to be primary convulsants.

2. Effects of Graded, Intraperitoneal Doses of the Boranes and Reserpine on Conscious Dogs.

The effects of the boranes on intact, unanesthetized dogs appeared similar to patterns produced by tranquilizers. Incomplete anesthesia, excitement, and convulsions in otherwise depressed animals are also seen after atropine, scopolamine (Ref. 12), reserpine (Ref. 13), the phenothiazines, and other antihistamines.

Striking miosis, after pentaborane exposure was previously noted by Weir et al. (Ref. 5). The nictitating membrane relaxation and ptosis seen during this series of experiments provided clear evidence of decreased sympathetic activity and suggested reserpine-like action of the boranes. These observations directed the design of experiments with anesthetized dogs.

Comparison of the behavioral effects of pentaborane, decaborane, and reserpine shows qualitative and quantitative differences as well as similarities.

- a. Under the specified conditions, pentaborane produces convulsions while the other compounds do not.
- b. Pentaborane produces less depression than decaborane or reserpine.
- c. Aggression was pronounced with pentaborane, slight with reserpine, and absent with decaborane.

d. The boranes act more rapidly and have shorter duration of action than reserpine.

A summary of these data is presented in Table V.

3. Cardiovascular and Autonomic Effects in Anesthetized and Conscious Dogs.

Cardiovascular and other autonomic effects are highly similar for all three agents. Sympathetic activity is limited, allowing the parasympathetic system to predominate. The initial rise in blood pressure produced by reserpine injection is due to liberation of norepinephrine into the circulatory system. Subsequent depletion of norepinephrine together with other undefined actions account for the later effects.

The main effects of the boranes studied were demonstrably different from other drug classes producing ganglionic blockade, adrenergic blockade, parasympatholytic, and parasympathomimetic actions, etc.

The failure of tyramine to exert its expected effect is presumptive evidence that norepinephrine has been depleted peripherally as well as centrally. This fact was used to differentiate the action of the boranes from that of triethyltin and other agents which affect only monamines of the central nervous system. The restitution of tyramine action by norepinephrine infusion is due to the uptake of the amine by the depleted sites. After reserpine injection, significant uptake of the injected amine takes place only after 72 hours (Ref. 14). Thus, the boranes have a much less persistent effect than reserpine, and however potent in liberating amines, do not block uptake.

4. Effects of the Boranes and Reserpine on the Monamines in the Central Nervous System of Rats.

Each of the three compounds deplete central nervous system serotonin and norepinephrine but there are differences. When pentaborane has markedly depleted serotonin, norepinephrine is much less depressed. Decaborane, in contrast, can produce nearly 70% depletion of norepinephrine after three hours, when serotonin is not yet significantly depressed (Figure 2).

Ability to deplete central nervous system amines does not establish similarity of boranes to reserpines since many drugs share this characteristic action. The boranes may be compared to other drugs on the same bases as to reserpine. For example, triethyltin causes no depletion of amines outside the central nervous system. Therefore, none of the profound peripheral effects appear as previously described. Similarly, tetrabenazine, a benzoquinolizine derivative, has a duration of action similar to the boranes, but causes no bradycardia, and shows a more persistent effect on brain norepinephrine than either reserpine or the boranes (Ref. 16). Action of the decarboxylase inhibitors (alpha-methyl-dopa or alpha-methyl--meta-tyrosine) leads to lower levels of central nervous system amines, but the evidence of initial liberation, rapid onset, and profound sedation seen with the boranes is absent. A modified reserpine, dimethylaminobenzoylmethyl reserpate (SU-5171) has selective action in liberating norepinephrine and may provide the closest comparison to decaborane (Ref. 17).

Table V

Comparison of Behavioral and Physiologic Effects of Pentaborane, Decaborane,
and Reserpine under Conditions of This Study

<u>Effect</u>	<u>Compound</u>		
	Pentaborane	Decaborane	Reserpine
Convulsions	+	0	0
Aggression	++	0	+
Ataxia	+	+	+
Depression	+	+++	++
Tranquility	+	+	+
Emesis	++	+	+
Diarrhea	++	+	+++
Injection of gingiva and conjunctiva, ptosis, and miosis	+		
Nictitating membrane relaxation	+	+	+
Muscle rigidity	+	0	
Hypotension, bradycardia	+	+	+

+ Slight
 ++ Moderate
 +++ Marked
 0 Not observed

In a study of SU-5171, Brodie et al. concluded that lack of sedation when norepinephrine levels were lowered, but serotonin levels were still high, reinforced his hypothesis that serotonin depletion rather than norepinephrine depletion produced sedation. The behavioral and chemical effects of decaborane in this laboratory do not support his conclusions. Decaborane consistently produced marked sedation in both rats and dogs during the first four hours after injection of the drug. It was during this time that, in rats, norepinephrine levels were lowest and serotonin levels were not significantly different from controls.

Pentaborane appears to have relatively greater ability to deplete serotonin. The greater potential of pentaborane for producing excitement and convulsions may be correlated with this property.

The differences between pentaborane and reserpine became less apparent after larger doses of the compounds. Convulsions after reserpine, for example, were not seen in this study, but may be demonstrated in dogs (Ref. 13). The ability of pentaborane to induce periods of aggressive, excited behavior is distinctive.

The comparatively simple inorganic structures of the boranes appear to be similar to reserpine. A steric similarity between the molecules of reserpine and pentaborane, a small, tetrahydral pyramid, is difficult to visualize. It may be important to establish whether the pharmacologic properties of the boranes are a function of their reducing abilities, but a survey of the literature on other reducing agents is inconclusive.

The analogous action between the boranes and reserpine permits further study of the boranes on the basis of the vast body of information already available on reserpine.

Earlier clinical descriptions of borane intoxication may be reinterpreted in terms of the pharmacology of tranquilizers. The cumulative effect of exposure to the boranes is explicable as progressive depletion.

Several obvious protection studies are suggested. Unlike the studies of reserpine which are designed primarily to demonstrate biochemical repair and antagonism of sedation, effort to protect against the boranes must also aim to prevent convulsions.

Injection of pentaborane as a solution in oil is feasible. The demonstration of comparable effect and mechanism of the boranes whether inhaled or injected suggests that experimenters lacking inhalation exposure facilities may nevertheless study these interesting compounds.

REFERENCES

1. Miller, D.F., Tamas, A.A., Robinson, L., and E. Merriweather, Cumulative Effects of Borane Toxicity as Revealed by a New Clinical Test, Wright Air Development Division Technical Report 60-604, Wright-Patterson Air Force Base, Ohio, August 1960, AD 247 355.
2. Roush, G., Kent, B.M., and H.A. Volz, Research on Toxic Hazards of Pentaborane, Technical Documentary Report AMRL-TDR-62-109, Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, Ohio, September 1962, AD 289 889.
3. Lowe, H.J., and G. Freeman, "Boron Hydride Intoxication in Man", AMA Archives of Industrial Health, Vol 16, pp 523-533, 1957.
4. Cordasco, E.M., "Pulmonary Aspects of Some Toxic Experimental Space Fuels", Diseases of the Chest, Vol 41, No 1, pp 68-74, 1962.
5. Weir, F.W., Seabaugh, V.M., Mershon, M.M., Burke, D.G., and H. Weeks, "Short Exposure Inhalation Toxicity of Pentaborane in Animals", Toxicology and Applied Pharmacology, Vol 6, pp 121-131, 1964.
6. Dost, F. N., D. J. Reed and C. H. Wang, Lethality of Pentaborane-9 in Mammalian Animals, Aerospace Medical Research Laboratories Technical Documentary Report AMRL-TDR-63-128, Wright-Patterson AFB, Ohio, December 1963, AD 431 218.
7. Bogdanski, D.F., Pletscher, A., Brodie, B.B., and S. Udenfriend, "Identification and Assay of Serotonin in Brain", The Journal of Pharmacology and Experimental Therapeutics, Vol 117, p 82, 1956.
8. Shore, P.A. and J.S. Olin, "Identification and Chemical Assay of Norepinephrine in Brain and Other Tissues", The Journal of Pharmacology and Experimental Therapeutics, Vol 122, pp 295-300, 1958.
9. Callingham, B.A. and R. Cass, "The Determination of Catecholamines in Biological Materials", The Clinical Chemistry of Monamines, pp 19-30, Elsenier Publishing Co., New York, 1963.
10. McNemar, Quinn, Psychological Statistics, Wiley, New York, 1949.
11. Litchfield, J.T., Jr., and F. Wilcoxon, "A simplified method of evaluating dose-effect experiments," The Journal of Pharmacology and Experimental Therapeutics, 95 (2) 1949.
12. Meyers, F.H. and B.E. Abreu, "A Comparison of the Central and Peripheral Effects of Atropine, Scopolamine and Some Synthetic Atropine-like Compounds", The Journal of Pharmacology and Experimental Therapeutics, Vol 104, pp 387-392, 1952.

13. Schneider, J.A., Woodson, R.E. and others, "The Pharmacology of Rauwolfia", Rauwolfia, p 119, Little, Brown & Co., Boston, 1957.
14. Bhagat, B. and F.E. Shideman, "Repletion of Cardiac Catecholamines in the Rat: Importance of the Adrenal Medulla and Synthesis from Precursors", The Journal of Pharmacology and Experimental Therapeutics, Vol 143, pp 77-81, 1964.
15. Shore, P.A., "Release of Serotonin and Catecholamines by Drugs", Pharmacological Reviews, Vol 14, pp 531-600, 1962.
16. Pletscher, A., Brossi, A., and K.F. Gey, "Benzoquinolizine Derivatives:" International Review of Neurology, Vol 4, pp 275-306, 1962.
17. Brodie, B.B., Firger, K.F., Orlans, F.B., Quinn, G.P., and F. Sulser, "Evidence that Tranquilizing Action of Reserpine is Associated with Change in Brain Serotonin and Not in Brain Norepinephrine", The Journal of Pharmacology and Experimental Therapeutics, Vol 129, pp 250-256, 1960.

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DOCUMENT CONTROL DATA - R&D <small>(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)</small>		
1. ORIGINATING ACTIVITY (Corporate author) The Hine Laboratories, Inc. 1099 Folsom Street San Francisco, California		2a. REPORT SECURITY CLASSIFICATION <div style="text-align: center; padding: 5px;">UNCLASSIFIED</div> 2b. GROUP <div style="text-align: center; padding: 5px;">n/a</div>
3. REPORT TITLE <div style="text-align: center; padding: 10px;">THE SIMILAR PHARMACOLOGIC AND TOXIC EFFECTS OF PENTABORANE, DECABORANE, AND RESERPINE</div>		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates) <div style="text-align: center; padding: 5px;">Final report, September 1963 - September 1964</div>		
5. AUTHOR(S) (Last name, first name, initial) <div style="display: flex; justify-content: space-between; padding: 10px 0;"><div style="text-align: center;">Weir, Francis W. Meyers, Frederick H.</div><div style="text-align: center;">Arbuckle, Robert H. Bennett, Swanson</div></div>		
6. REPORT DATE <div style="text-align: center; padding: 5px;">May 1965</div>	7a. TOTAL NO. OF PAGES <div style="text-align: center; padding: 5px;">19</div>	7b. NO. OF REFS <div style="text-align: center; padding: 5px;">17</div>
8a. CONTRACT OR GRANT NO. AF 33(657)-11756 b. PROJECT NO 6302 c. Task No. 630202 d.		9a. ORIGINATOR'S REPORT NUMBER(S) <div style="text-align: center; padding: 10px;">None</div> 9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report) <div style="text-align: center; padding: 5px;">AMRL-TR-65-49</div>
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